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EXAMINER	
EINSMANN, J	
ART UNIT	**PAPER NUMBER**
1655	14

DATE MAILED: 01/30/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/336,609	BOLES ET AL.	
	Examiner	Art Unit	
	Juliet C. Einsmann	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-63* is/are pending in the application.

4a) Of the above claim(s) *44-50* is/are withdrawn from consideration.

5)☐ Claim(s) *42,43 and 63* is/are allowed.

6)☒ Claim(s) *1-41 and 51-62* is/are rejected.

7)☒ Claim(s) *42,43 and 63* is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☒ Interview Summary (PTO-413) Paper No(s). 9 .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

1. This action is written in response applicant's correspondence submitted 11/8/00, paper number 13. Claims 1, 20-22, 24, 26-32, 41, and 42 have been amended and claims 51-63 have been added. Claims 1-63 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Claim Rejections - 35 USC § 112

2. Claims 14, 16, 18, 36, 38, and 40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are drawn to detection methods using the SRP RNA from organisms belonging to specifically listed genuses of protozoa, fungi and bacteria. The practice of this invention requires knowledge of the specific sequences of the SRP RNA of these organisms in order to design probes for use in their detection. The specification does not provide specific disclosure of the sequences of SRP RNA for these genuses, and further, these sequences would not have been known to one of ordinary skill in the art at the time the invention was made because Zwieb et al. (Nucleic Acids Research, 2000, Vol. 28, No. 1 (171-172)) teach all known SRP RNA sequences and these species are not included in their database. Furthermore and extensive search of commercial databases revealed that these sequences are not disclosed in the prior art. As such, the specification lacks sufficient

written description of the claimed invention. With regard to claim 18, the examiner is aware that the SRP RNA sequences for some of the claimed genuses are available in the prior art (*Bacillus*, *Pseudomonas, Chlamydia, Chlostridia, Escherichia, Helicobacter, Legionella, Haemophilus*, *Trypanosoma,* and *Ureaplasma*), and these are considered to have met the written description requirement. This rejection applies to claims 16, 18, 38, and 40 with regard to those groups claimed for which there has been no disclosure of the appropriate nucleic acid sequences either in the instant specification or in the prior art.

Response to Remarks

Applicant traverses this rejection on the basis that Applicant has provided sufficient information with regard to the physical and structural features of the SRP RNA sequences in question to render them properly described. The examiner respectfully disagrees. The specific sequences of the SRP RNA's of the groups to be identified in the rejected claims are in fact not described in the specification or the prior art, and these sequences are essential to practice the invention. The issue at hand is not whether the ordinary practitioner might have been able to obtain the sequences, it is whether the instant inventors had possession of the claimed invention at the time the application was filed. Applicant cites as support for the traversal the case of *University of California v. Eli Lilly*. In that case it was determined that the specification did not provide adequate written description of a cDNA encoding human insulin because, "While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA." Even though, in that case the

closely related rat cDNA was disclosed, the court none the less found that "Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent."

In the instant case, the disclosure that these SRP RNA's exist in many organisms, the disclosure of some SRP RNA's, and the suggestion that the SRP RNA may be conserved among organisms is not considered sufficient to describe the SRP RNA necessary to carry out the invention for the detection of the genuses whose SRP RNA sequences are not known .

Applicant further points out that a cited web site and paper given in the specification provide the sequences for a great number of SRP RNA sequences. The examiner acknowledges this disclosure in the prior art, and with regard to those nucleic acid sequences the claims are considered described, as noted in the rejection above. This rejection is applied in so far as the rejected claims recite specific groups of organisms (genuses) whose SRP RNA sequences are not disclosed herein or in the prior art.

Claim Rejections - 35 USC § 103

The following rejections are reiterated in the case of the previously pending claims and are applied as appropriate to the claims added in the amendment submitted 11/8/00.

3. Claims 1-2, 4-8, 10, 12, 17-19, 52, 53, 56, 57, and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. (US 5595874) in view of Nakamura et al. (Nucleic Acids Research 20(19): 5227-5228).

Hogan et al. teach methods for the identification of non-viral organisms in samples, including human blood samples (Col. 1, line 30) using hybridization probes to RNA. This method comprises the steps of (i) contacting a sample with more than one labeled nucleic acid probe (Col. 28, lines 1-8, 18-21) (ii) incubating the sample comprising the sample and the RNA under conditions to allow a hybrid to form (Col. 28, lines 25-27) and (iii) detecting the hybridization products (Col. 28, lines 35-40). The probes taught by Hogan et al. include DNA probes (Col. 8, line 20). Furthermore, Hogan et al. provide specific instructions for the selection of probes:

> "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.
>
> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided (Col. 6, line 50-Col. 7, line11)."

Hogan et al. do not teach the use of this method using SRP RNA to detect a group of non-viral organisms.

Nakamura et al. teach sequence of the SRP RNA (the scRNA) for ten species of *Bacillus*, and further provide an alignment of these sequences (see Fig. 1). Nakamura et al. point out that there is a block containing complete primary sequence identity which corresponds to nucleotides 154-175 of the *B. subtilis* scRNA (p. 5227). Instantly disclosed SEQ ID NO: 2 consists of the reverse complement of nucleotides 154-175 of the *B. subtilis* sequence, and instantly disclosed SEQ ID NO: 3, 4 , and 5 are smaller portions of this region.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the SRP RNA taught by Nakamura et al. in the detection method taught by Hogan et al. In light of the combined teachings of Nakamura et al. and the clear teachings on probe selection from as well as the methods taught by Hogan et al. the ordinary practitioner would have been motivated to select a probe from the 21 base pair conserved region of the *Bacillus* genome in order to have created a rapid and effective method for detecting *Bacillus*. One would be motivated to detect *Bacillus* in a sample, and particularly a human sample since it is well known in the art that some species of *Bacillus* are pathogenic to humans, for example *B. cerus*. The combination of the teachings of Hogan et al. with those of Nakamura et al. would have resulted in a rapid and effective method for detecting *Bacillus* in a sample.

4. Claims 1-2, 4-8, 10-12, 17-19, 52, 53, 56, 57, and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. (US 5595874) in view Griffin (Journal of Biological Chemistry (1975) 250(14):5426-5437).

Hogan et al. teach methods for the identification of non-viral organisms in samples, including human blood samples (Col. 1, line 30) using hybridization probes to RNA. This method comprises the steps of (i) contacting a sample with more than one labeled nucleic acid probe (Col. 28, lines 1-8, 18-21) (ii) incubating the sample comprising the sample and the RNA under conditions to allow a hybrid to form (Col. 28, lines 25-27) and (iii) detecting the hybridization products (Col. 28, lines 35-40). The probes taught by Hogan et al. include DNA probes (Col. 8, line 20). Furthermore, Hogan et al. provide specific instructions for the selection of probes:

> "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.
>
> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided (Col. 6, line 50-Col. 7, line11)."

Hogan et al. do not teach the use of this method using SRP RNA to detect a group of non-viral organisms.

Griffin teaches sequence of 4.5 S RNA from *E. coli* (Abstract, Fig. 10) and that the 4.5 S RNA has been shown to be a component of a number of strains of E. coli. Instant SEQ ID NO: 6 consists of the reverse complement of nucleotides 37-59 of this sequence, instant SEQ ID NO: 22 consists of the reverse complement of nucleotides 40-52, and instant SEQ ID NO: 9 consists of the reverse complement of nucleotides 65-82. Therefore, the 110 base pair RNA disclosed by Griffin comprises instant SEQ ID NO: 6, 22, and 9.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the 4.5 S RNA taught by Griffin as a probe for the detection of E. coli in the methods taught by Hogan et al. in order to have created a method for the detection of E. coli. The ordinary practitioner would have been motivated to have used the SRP RNA because Griffin teaches that this RNA has been shown to be a component of a number of strains of E. coli. Furthermore, the ordinary practitioner would have been motivated to detect E. coli in a sample, including a human sample, because it is well known in the art that some E. coli are pathogenic to humans. With regard to the length limitations of claims 6 and 7, the use of any smaller probes would have also been obvious to one of skill in the art, as these would be considered functional homologues of the 100-mer oligonucleotide taught by Griffin since they also would be considered to have the functional property of being able to detect E. coli.

5. Claims 1-2, 4-8, 10-13, 17-19, 52, 53, 56, 57, and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. (US 5595874) in view of Larsen et al. (Nucleic Acids Research 19(2) 209-215).

Hogan et al. teach methods for the identification of non-viral organisms in samples, including human blood samples (Col. 1, line 30) using hybridization probes to RNA. This method comprises the steps of (i) contacting a sample with more than one labeled nucleic acid probe (Col. 28, lines 1-8, 18-21) (ii) incubating the sample comprising the sample and the RNA under conditions to allow a hybrid to form (Col. 28, lines 25-27) and (iii) detecting the hybridization products (Col. 28, lines 35-40). The probes taught by Hogan et al. include DNA probes (Col. 8, line 20). Furthermore, Hogan et al. provide specific instructions for the selection of probes:

> "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.
>
> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided (Col. 6, line 50-Col. 7, line11)."

Hogan et al. do not teach the use of this method using SRP RNA to detect a group of non-viral organisms.

Larsen et al. teach the sequences of SRP RNA from 39 species of organisms, including the 4.5S RNA of E. coli. Instant SEQ ID NO: 6 consists of the reverse complement of nucleotides 37-59 of this sequence, instant SEQ ID NO: 22 consists of the reverse complement of nucleotides 40-52, and instant SEQ ID NO: 9 consists of the reverse complement of SEQ ID NO: 65-82. Therefore, the E. coli RNA disclosed by Larsen et al. comprises instant SEQ ID NO: 6, 22, and 9. Larsen et al. also teach the SRP RNA sequence from a fungus, specifically, the yeast *Schizosaccaromyces pombe*.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the alignment provided by Larsen et al. and the clear instructions on probe selection provided by Hogan et al. in order to have selected probes useful in the methods taught by Hogan et al. for the detection of any one of the species disclosed by Larsen et al. It would have been further obvious to have used such probes to detect, for example, E. coli in humans since E. coli is well known in the art to be a pathogen to humans. An ordinary practitioner would have been motivated to develop such a detection assay in order to have provided a rapid method for screening for pathogens in samples. With regard to the length limitations of claims 6 and 7, the use of any smaller probes would have also been obvious to one of skill in the art, as these would be considered functional homologues of the 100-mer oligonucleotide taught by Larsen since they also would be considered to have the functional property of being able to detect E. coli.

6. Claims 1-2, 4-5, 10, 15-16, 52, 56, and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. (US 5595874) in view of Michaeli et al. (Molecular and Biochemical Parasitology, 51 (1992) 55-64).

Hogan et al. teach methods for the identification of non-viral organisms in samples, including human blood samples (Col. 1, line 30) using hybridization probes to RNA. This method comprises the steps of (i) contacting a sample with more than one labeled nucleic acid probe (Col. 28, lines 1-8, 18-21) (ii) incubating the sample comprising the sample and the RNA under conditions to allow a hybrid to form (Col. 28, lines 25-27) and (iii) detecting the hybridization products (Col. 28, lines 35-40). The probes taught by Hogan et al. include DNA probes (Col. 8, line 20). Furthermore, Hogan et al. provide specific instructions for the selection of probes:

> "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.
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> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form

strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided (Col. 6, line 50-Col. 7, line11)."

Hogan et al. do not teach the use of this method using SRP RNA to detect a group of non-viral organisms.

Michaeli et al. teach the sequence of the 7SL SRP RNA of *Trypansoma brucei,* a unicellular parasitic protozoa (Fig. 3), and teach that 7SL RNA's are divergent at their primary sequence levels among different groups of eukaryotes (p. 56).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the SRP RNA of *Trypansoma brucei* as a probe in the methods taught by Hogan et al. in order to have developed a rapid and effective method for detecting a parasitic protozoan in samples.

7. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over any one of the following:

(A) Hogan et al. in view of Nakamura et al. as applied to claims 1-2, 4-8, 10, 12, 17-19, 52, 53, 56, 57, and 58 above, and further in view of Rudert et al.

(B) Hogan et al. in view of Griffin et al. as applied to claims 1-2, 4-8, 10-12, 17-19, 52, 53, 56, 57, and 58above, and further in view of Rudert et al.

(C) Hogan et al. in view of Larsen et al. as applied to claims 1-2, 4-8, 10-13, 17-19, 52, 53, 56, 57, and 58 above, and further in view of Rudert et al.

(D) Hogan et al. in view of Michaeli et al. as applied to claims 1-2, 4-5, 10, 15-16, 52, 56, and 57 above, and further in view of Rudert et al.

The teachings of all of the above combinations are applied to this rejection as outlined above. These teachings do not teach methods in which the SRP RNA is labeled.

Rudert et al. teach that the reverse dot blot technique is useful for detecting nucleic acid sequences, and that in this technique sample nucleic acids are labeled and hybridized to probes bound to a solid support (Col. 3, lines 1-5).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used a dot-blot technique in the methods taught by reference combinations A-D and thus have labeled the SRP RNA. An ordinary practitioner would have been motivated to use such a technique because Rudert et al. specifically teach that the reverse dot blot technique has advantages which include the ability to screen with many specific probes at the same time simultaneously and in the same container, only one preparation is required to label a large amount of sample nucleic acid and thus, simple and direct comparison of the results between different probes is possible (Col. 3, lines 10-26).

8. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over any one of the following:

(A) Hogan et al. in view of Nakamura et al. as applied to claims 1-2, 4-8, 10, 12, 17-19, 52, 53, 56, 57, and 58 above, and further in view of Rudert et al.

(B) Hogan et al. in view of Griffin et al. as applied to claims 1-2, 4-8, 10-12, 17-19, 52, 53, 56, 57, and 58 above, and further in view of Rudert et al.

(C) Hogan et al. in view of Larsen et al. as applied to claims 1-2, 4-8, 10-13, 17-19, 52, 53, 56, 57, and 58 above, and further in view of Rudert et al.

(D) Hogan et al. in view of Michaeli et al. as applied to claims 1-2, 4-5, 10, 15-16, 52, 56, and 57 above, and further in view of Rudert et al.

The teachings of all of the above combinations are applied to this rejection as outlined above. The previously cited references do not teach methods in the nucleic acid probe is a PNA.

Buchardt et al. teach that "peptide nucleic acids (PNAs) are novel DNA mimics in which the sugar-phosphate backbone has been replaced with a backbone based on amino acids (abstract)."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used PNA probes as taught by Buchardt et al. in the method taught by any one of A-D listed above in order to have provided a more sensitive method for the detection of the SRP RNA since Buchardt et al. teach that PNAs "exhibit sequence-specific binding to DNA and RNA with higher affinities and specificities than unmodified DNA. They are resistant to nuclease and protease attack in serum and cellular extracts and, thus, appear very promising as diagnostic and biomolecular probes (abstract)."

9. Claims 20-22, 24-25, 28-30, 32, 34, 39-41, 54, 55, and 59-61 rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. in view of Nakamura et al. as applied to claims 1-2, 4-8, 10, 12, 17-19, 52, 53, 56, 57, and 58 above, and further in view of Jiro (JP H3[1991]-47094(A)).

The teachings of Hogan et al. in view of Nakamura et al. are applied to this rejection as they are applied above. Hogan et al. in view of Nakamura et al. do not teach contacting the duplex SRP RNA with a gel-immobilized nucleic acid probe and detecting the hybridization

product. The further do not teach a step which comprises electrophoresing the sample through a gel.

Jiro teaches a method for detecting nucleic acids in which a nucleic acid probe is fixed on an electrophoretic carrier (the gel-immobilized probe), the sample is moved through the electrophoretic carrier by electrophoresis, and a hybridization reaction results (p. 6, second paragraph). A second labeled nucleic acid probe is then moved through the electrophoretic carrier which binds with a portion of the sample that did not bind to the first probe, and the labeled portion of the second nucleic acid probe is detected as an indication of a hybridization reaction (p. 6). Jiro further teaches that the use of electrophoresis in hybridization assays is beneficial because the DNA sample undergoes forced movement within the electrophoretic carrier and this permits the hybridization reaction to take place more rapidly than if the sample underwent passive diffusion (p. 11).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have included a capture step which employed gel-immobilized probe hybridization using electrophoresis as taught by Jiro et al. in the method taught by Hogan et al. in view of Nakamura et al. The ordinary practitioner would have been motivated to include such a step in order to have provided a more rapid and effective method for detecting nucleic acids in a sample, since Jiro specifically teaches the benefits of using the electrophoretic methodology, "because the DNA fragment sample undergoes forced movement within the electrophoretic carrier by means of electrophoresis, this permits the hybridization reaction to take place more rapidly (p. 11)". With regard to the difference in the order that the instant claim completes the

steps as compared to the teachings of Jiro et al., according to MPEP 2144.06, "selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results". In this case, it would have been obvious to capture the combination of the detection probe and the target either in sequence as expressly shown by Jiro, or by first combining the reagents into a duplex, as is well known in the art, because performing the process steps in an altered order, both of which orders are known in the art, is prima facie obvious in the absence of a secondary consideration such as unexpected results.

10. Claims 20-22, 24-25, 28-30, 32-34, 39-41, 54, 55 and 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. in view of Griffin et al. as applied to claims 1-2, 4-8, 10-12, 17-19, 52, 53, 56, 57, and 58 above, and further in view of Jiro (JP H3[1991]-47094(A)).

The teachings of Hogan et al. in view of Griffin et al. are applied to this rejection as they are applied above. Hogan et al. in view of Griffin et al. do not teach contacting the duplex SRP RNA with a gel-immobilized nucleic acid probe and detecting the hybridization product. The further do not teach a step which comprises electrophoresing the sample through a gel.

Jiro teaches a method for detecting nucleic acids in which a nucleic acid probe is fixed on an electrophoretic carrier (the gel-immobilized probe), the sample is moved through the electrophoretic carrier by electrophoresis, and a hybridization reaction results (p. 6, second paragraph). A second labeled nucleic acid probe is then moved through the electrophoretic carrier which binds with a portion of the sample that did not bind to the first probe, and the labeled portion of the second nucleic acid probe is detected as an indication of a hybridization

reaction (p. 6). Jiro further teaches that the use of electrophoresis in hybridization assays is beneficial because the DNA sample undergoes forced movement within the electrophoretic carrier and this permits the hybridization reaction to take place more rapidly than if the sample underwent passive diffusion (p. 11).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have included a capture step which employed gel-immobilized probe hybridization using electrophoresis as taught by Jiro et al. in the method taught by Hogan et al. in view of Griffin et al. The ordinary practitioner would have been motivated to include such a step in order to have provided a more rapid and effective method for detecting nucleic acids in a sample, since Jiro specifically teaches the benefits of using the electrophoretic methodology, "because the DNA fragment sample undergoes forced movement within the electrophoretic carrier by means of electrophoresis, this permits the hybridization reaction to take place more rapidly (p. 11)". With regard to the difference in the order that the instant claim completes the steps as compared to the teachings of Jiro et al., according to MPEP 2144.06, "selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results". In this case, it would have been obvious to capture the combination of the detection probe and the target either in sequence as expressly shown by Jiro, or by first combining the reagents into a duplex, as is well known in the art, because performing the process steps in an altered order, both of which orders are known in the art, is prima facie obvious in the absence of a secondary consideration such as unexpected results.

11. Claims 20-22, 24-25, 28-30, 32-35, 39-41, 54, 55 and 59-61 rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. in view of Larsen et al. as applied to claims 1-2, 4-8, 10-13, 17-19, 52, 53, 56, 57, and 58 above, and further in view of Jiro (JP H3[1991]-47094(A)).

The teachings of Hogan et al. in view of Larsen et al. are applied to this rejection as they are applied above. Hogan et al. in view of Larsen et al. do not teach contacting the duplex SRP RNA with a gel-immobilized nucleic acid probe and detecting the hybridization product. The further do not teach a step which comprises electrophoresing the sample through a gel.

Jiro teaches a method for detecting nucleic acids in which a nucleic acid probe is fixed on an electrophoretic carrier (the gel-immobilized probe), the sample is moved through the electrophoretic carrier by electrophoresis, and a hybridization reaction results (p. 6, second paragraph). A second labeled nucleic acid probe is then moved through the electrophoretic carrier which binds with a portion of the sample that did not bind to the first probe, and the labeled portion of the second nucleic acid probe is detected as an indication of a hybridization reaction (p. 6). Jiro further teaches that the use of electrophoresis in hybridization assays is beneficial because the DNA sample undergoes forced movement within the electrophoretic carrier and this permits the hybridization reaction to take place more rapidly than if the sample underwent passive diffusion (p. 11).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have included a capture step which employed gel-immobilized probe hybridization using electrophoresis as taught by Jiro et al. in the method taught by Hogan et al. in

view of Larsen et al. The ordinary practitioner would have been motivated to include such a step in order to have provided a more rapid and effective method for detecting nucleic acids in a sample, since Jiro specifically teaches the benefits of using the electrophoretic methodology, "because the DNA fragment sample undergoes forced movement within the electrophoretic carrier by means of electrophoresis, this permits the hybridization reaction to take place more rapidly (p. 11)". With regard to the difference in the order that the instant claim completes the steps as compared to the teachings of Jiro et al., according to MPEP 2144.06, "selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results". In this case, it would have been obvious to capture the combination of the detection probe and the target either in sequence as expressly shown by Jiro, or by first combining the reagents into a duplex, as is well known in the art, because performing the process steps in an altered order, both of which orders are known in the art, is prima facie obvious in the absence of a secondary consideration such as unexpected results.

12. Claims 20-22, 24-25, 32, 37-38, 54, 59, and 61 rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. in view of Michaeli et al. as applied to claims 1-2, 4-5, 10, 15-16, 52, 56, and 57 above, and further in view of Jiro (JP H3[1991]-47094(A)).

The teachings of Hogan et al. in view of Michaeli et al. are applied to this rejection as they are applied above. Hogan et al. in view of Michaeli et al. do not teach contacting the duplex SRP RNA with a gel-immobilized nucleic acid probe and detecting the hybridization product. The further do not teach a step which comprises electrophoresing the sample through a gel.

Jiro teaches a method for detecting nucleic acids in which a nucleic acid probe is fixed on an electrophoretic carrier (the gel-immobilized probe), the sample is moved through the electrophoretic carrier by electrophoresis, and a hybridization reaction results (p. 6, second paragraph). A second labeled nucleic acid probe is then moved through the electrophoretic carrier which binds with a portion of the sample that did not bind to the first probe, and the labeled portion of the second nucleic acid probe is detected as an indication of a hybridization reaction (p. 6). Jiro further teaches that the use of electrophoresis in hybridization assays is beneficial because the DNA sample undergoes forced movement within the electrophoretic carrier and this permits the hybridization reaction to take place more rapidly than if the sample underwent passive diffusion (p. 11).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have included a capture step which employed gel-immobilized probe hybridization using electrophoresis as taught by Jiro et al. in the method taught by Hogan et al. in view of Michaeli et al. The ordinary practitioner would have been motivated to include such a step in order to have provided a more rapid and effective method for detecting nucleic acids in a sample, since Jiro specifically teaches the benefits of using the electrophoretic methodology, "because the DNA fragment sample undergoes forced movement within the electrophoretic carrier by means of electrophoresis, this permits the hybridization reaction to take place more rapidly (p. 11)". With regard to the difference in the order that the instant claim completes the steps as compared to the teachings of Jiro et al., according to MPEP 2144.06, "selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected

results". In this case, it would have been obvious to capture the combination of the detection probe and the target either in sequence as expressly shown by Jiro, or by first combining the reagents into a duplex, as is well known in the art, because performing the process steps in an altered order, both of which orders are known in the art, is prima facie obvious in the absence of a secondary consideration such as unexpected results.

13. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over any one of the following:

(A) Hogan et al. in view of Nakamura et al. as applied to claims 20-22, 24-25, 28-30, 32-35, 39-41, 54, 55 and 59-61 above, and further in view of Rudert et al.

(B) Hogan et al. in view of Griffin et al. as applied to claims 20-22, 24-25, 28-30, 32-35, 39-41, 54, 55 and 59-61 above, and further in view of Rudert et al.

(C) Hogan et al. in view of Larsen et al. as applied to claims 20-22, 24-25, 28-30, 32-35, 39-41, 54, 55 and 59-61 above, and further in view of Rudert et al.

(D) Hogan et al. in view of Michaeli et al. as applied to claims 20-22, 24-25, 32, 37-38, 54, 59, and 60 above, and further in view of Rudert et al.

The teachings of all of the above combinations are applied to this rejection as outlined above. These teachings do not teach methods in which the SRP RNA is labeled.

Rudert et al. teach that labeling sample nucleic acid as opposed to probes is advantageous because it simplifies the assay process by allowing the ability to screen samples with many different probes at once (Col. 3, lines 10-26).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used a dot-blot technique in the methods taught by reference combinations A-D and thus have labeled the SRP RNA. An ordinary practitioner would have been motivated to use such a technique because Rudert et al. specifically teach that the reverse dot blot technique has advantages which include the ability to screen with many specific probes at the same time simultaneously and in the same container, only one preparation is required to label a large amount of sample nucleic acid and thus, simple and direct comparison of the results between different probes is possible (Col. 3, lines 10-26).

14. Claims 26 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of the following:

(A) Hogan et al. in view of Nakamura et al. as applied to claims 20-22, 24-25, 28-30, 32-35, 39-41, 54, 55 and 59-61 above, and further in view of Urdea et al.

(B) Hogan et al. in view of Griffin et al. as applied to claims 20-22, 24-25, 28-30, 32-35, 39-41, 54, 55 and 59-61 above, and further in view of Urdea et al.

(C) Hogan et al. in view of Larsen et al. as applied to claims 20-22, 24-25, 28-30, 32-35, 39-41, 54, 55 and 59-61 above, and further in view of Urdea et al.

(D) Hogan et al. in view of Michaeli et al. as applied to claims 20-22, 24-25, 32, 37-38, 54, 59, and 60 above, and further in view of Urdea et al.

The teachings of all of the above combinations are applied to this rejection as outlined above. These teachings do not teach methods in which the nucleic acid probe is an adaptor probe comprising a subsequence of that hybridizes to the gel-immobilized probe.

Urdea et al. teach nucleic acid sandwich assays which utilize an adaptor probe which has regions that hybridize to both the sample and the immobilized probe (Col. 1, lines 50-53).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the probe taught by Urdea et al. in any one of the methods taught by A-D in order to have provided a more efficient capture based detection method since Urdea et al. teach that such a method is advantageous because "using combinations of nucleic acid sequences complementary to a nucleic acid analyte and to arbitrary sequences and specific binding pair members, a detectable label may be separated in two phases in proportion to he amount of analyte present in the sample (Col. 2, lines 29-24)."

15. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over any one of the following:

(A) Hogan et al. in view of Nakamura et al. as applied to claims 20-22, 24-25, 28-30, 32-35, 39-41, 54, 55 and 59-61 above, and further in view of Buchardt et al.

(B) Hogan et al. in view of Griffin et al. as applied to claims 20-22, 24-25, 28-30, 32-35, 39-41, 54, 55 and 59-61 above, and further in view of Buchardt et al.

(C) Hogan et al. in view of Larsen et al. as applied to claims 20-22, 24-25, 28-30, 32-35, 39-41, 54, 55 and 59-61 above, and further in view of Buchardt et al.

(D) Hogan et al. in view of Michaeli et al. as applied to claims 20-22, 24-25, 32, 37-38, 54, 59, and 60 above, and further in view of Buchardt et al.

The teachings of all of the above combinations are applied to this rejection as outlined above. The previously cited references do not teach methods in the nucleic acid probe is a PNA.

Buchardt et al. teach that "peptide nucleic acids (PNAs) are novel DNA mimics in which the sugar-phosphate backbone has been replaced with a backbone based on amino acids (abstract)."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used PNA probes as taught by Buchardt et al. in the method taught by any one of A-D listed above in order to have provided a more sensitive method for the detection of the SRP RNA since Buchardt et al. teach that PNAs "exhibit sequence-specific binding to DNA and RNA with higher affinities and specificities than unmodified DNA. They are resistant to nuclease and protease attack in serum and cellular extracts and, thus, appear very promising as diagnostic and biomolecular probes (abstract)."

Response to Remarks

Applicant traverses the obviousness rejections on the grounds that the rejection failed to indicate that one of skill in the art would have had a reasonable expectation of success using SRP RNA as a target for detecting selected non-viral organisms. Applicant correctly point out that the instant claims are drawn to the use of SRP RNA while the teachings of Hogan *et al.* disclose the use of ribosomal RNA for the detection of non-viral organisms. Applicant supports the argument that there is no reasonable expectation of success by pointing out that Hogan does not provide any evidence or indication that one of skill in the art would be successful using SRP RNA probes. This is not persuasive.

Absolute predictability is not required in order to establish an expectation of success. The MPEP states, "Obviousness does not require absolute predictability, however, at least some

degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness (2143.02)." In the instant case, applicant supported the argument that there was no reasonable expectation of success by pointing out that ribosomal RNA and SRP RNA have different functions in cells, that SRP RNA is present in lower copy numbers in cells than rRNA and that SRP RNA has a more complicated secondary structure than ribosomal RNA. However, these are not persuasive to support the argument because the prior art concerning hybridization methods is vast, and includes great detail as to how to increase the sensitivity of a hybridization assay and how to avoid problems that might arise due to secondary structure of target nucleic acids. The fact that SRP RNA and rRNA have different functions in cells is irrelevant with regard to the ability to detect SRP RNA in a hybridization assay. In the instant case, while absolute predictability might not be present, the expectation of success is quite high considering the teachings of Hogan *et al.* concerning how to select probes and the disclosure of the SRP RNA sequences in the prior art, and the state of the prior art concerning hybridization assays.

Therefore, these rejections are maintained.

Allowable Subject Matter

16. Claims 42, 43 and 63 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

17. Instant SEQ ID NO: 24 consists of the reverse complement of nucleotides 159-171 of the P. aeruginosa 4.5 S RNA as disclosed in Brown et al. (J. Bacteriol. (1989) 171(12) 6517-6520). Therefore, the nucleic acid taught by Brown et al. comprises instant SEQ ID NO: 24.

Instantly disclosed SEQ ID NO: 7-11 are free of the prior art. SEQ ID NO: 21, 23, and 26 have not been previously disclosed in SRP RNA.

18. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

JEFFREY FREDMAN
PRIMARY EXAMINER

Juliet C. Einsmann
Examiner
Art Unit 1655

January 26, 2001